TREATMENT OF FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

RELATED APPLICATIONS

[0001] The instant application claims priority to U.S. Provisional Application No. 62/958,448, filed on Jan. 8, 2020; U.S. Provisional Application No. 63/076,691, filed on Sep. 10, 2020; and U.S. Provisional Application No. 63/081,428, filed on Sep. 22, 2020, the entire contents of each of which are expressly incorporated herein by reference in their entireties.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Jan. 20, 2021, is named 118003-00604_SL.txt and is 18,393 bytes in size.

BACKGROUND

[0003] Fibrodysplasia ossificans progressiva (FOP), also known as Munchmeyer disease, is an autosomal dominant disorder characterized by early onset, episodic and progressive ossification of skeletal muscle and associated connective tissue. In FOP subjects, bone forms in soft tissue outside of the normal skeleton, a process known as heterotopic ossification (HO), which can lead to the development of a secondary skeleton and progressively restricts the patient's ability to move. Removal of the new bone formation has been shown to be ineffective and leads to the development of additional new bone growth.

[0004] FOP is driven by mutations in the intracellular domain of ACVR1 (ALK2), with the great majority altering Arginine 206 to Histidine (R206H) (Pignolo, R. J. et al. 2011, *Orphanet J. Rare Dis.* 6:80). ACVR1 is a type I receptor for bone morphogenic proteins (BMPs). The R206H mutation, among others, is believed to increase the sensitivity of the receptor to activation and render it more resistant to silencing.

[0005] Although certain types of drugs have been used to relieve pain and swelling associated with FOP during flare-ups, no effective medical treatment is currently known for FOP.

SUMMARY

[0006] The instant disclosure provides a method of treating Fibrodysplasia Ossificans Progressiva (FOP), comprising administering to a subject having FOP a therapeutically effective amount of an Activin A antagonist. In particular, the inventors of the instant application have surprisingly discovered, only after undertaking a phase II clinical trial in humans, that treatment of FOP subjects with an Activin A antagonist dramatically reduces and/or prevents the development of new heterotopic ossification (HO) bone growth, and reduced average rates of lesion growth and mineralization.

[0007] In one aspect the disclosure provides a method of treating fibrodysplasia ossificans progressiva (FOP), the method comprising administering to a human subject having FOP a therapeutically effective amount of an Activin A antagonist, thereby treating the FOP.

[0008] In some embodiments the Activin A antagonist is an anti-Activin A antibody or antigen-binding fragment thereof. In some embodiments, the antibody competes for binding with an antibody comprising the heavy and light chain variable regions of the antibody designated H4H10446P, H4H10430P or A1. In some embodiments, the antibody comprises the heavy and light chain variable regions of the antibody designated H4H10446P, H4H10430P or A1. In some embodiments, the antibody is a chimeric, veneered, humanized or human antibody. In some embodiments, the antibody is an intact antibody. In some embodiments, the antibody is a human kappa IgG1 antibody. In some embodiments, the antibody is administered in combination therapy with an ACVR1, ACVR2A, or ACVR2B extracellular domain-Fc fusion protein.

[0009] The disclosure further provides an antagonist of Activin A for use in a method of treating Fibrodysplasia Ossificans Progressiva (FOP), the method comprising administering to a subject having FOP a therapeutically effective amount of the antagonist of Activin A. Optionally, the Activin A antagonist is an anti-Activin A antibody or antigen-binding fragment thereof. Optionally, the disclosure provides the use of an anti-Activin A antibody or antigen-binding fragment thereof in the manufacture of a medicament for treating FOP. Optionally, the antibody is chimeric, veneered, humanized or human antibody. Optionally, the antibody is an intact antibody. Optionally, the antibody is a human kappa IgG1 antibody. Optionally, the antibody is administered in combination therapy with an ACVR1, ACVR2A, or ACVR2B extracellular domain-Fc fusion protein.

[0010] In one aspect, the disclosure provides a method of decreasing the formation of new heterotopic ossification lesions in a human subject with FOP, the method comprising administering to the human subject a therapeutically effective amount of an Activin A antagonist, thereby decreasing the formation of new heterotopic ossification lesions in the human subject.

[0011] In one embodiment, the formation of new heterotopic ossification lesions is prevented in the human subject.

[0012] In one embodiment, the human subject exhibits a decrease in number of new heterotopic ossification lesions of at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 5%-90%, at least 10%-90%, at least 20%-90%, at least 30%-90%, at least 40%-90%, at least 50%-90%, at least 60%-90%, at least 70%-90%, at least 80%-90%, at least 5%-80%, at least 5%-70%, at least 5%-60%, at least 5%-50%, at least 5%-40%, at least 5%-30%, at least 5%-20%, or at least 5%-10%, relative to a control.

[0013] In one embodiment, the human subject exhibits a decrease in new heterotopic ossification lesion volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 5%-50%, at least 10%-50%, at least 20%-50%, at least 30%-50%, at least 40%-50%, at least 5%-40%, at least 5%-30%, at least 5%-20%, or at least 5%-10%, relative to a control.

[0014] In one embodiment, the human subject exhibits a decrease in a rate of new heterotopic ossification lesion growth and mineralization of at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 5%-50%, at least 10%-50%, at least 20%-50%, at least